REMARKS/ARGUMENTS

Examiners Kishore and Pulliam are thanked for the courtesy extended to applicant's undersigned attorney during the telephone interview of June 10, 2003. While no agreement could be reached, the interview was useful in clarifying certain of the issues.

Claims 37 to 40 have been introduced into the application. These claims are based on the disclosure set forth in the specification as originally filed and particularly on pages 17 through 28 of the original application.

New claim 37 further defines the active ingredient and new claims 38 to 40 specifically recite that the pharmaceutical preparation is stable.

In Paper No. 20, the Examiner rejected claims 1 to 13 and 15 to 34 under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 6,132,771 to DePui et al. ("DePui"). Additionally, claims 1 to 13 and 15 to 36 were rejected under 35 U.S.C. §103(a) as unpatentable over DePui. It is submitted these rejections are improper and should be withdrawn.

These rejections were discussed during the June 10 telephone interview.

For a reference to anticipate a claimed invention, that single reference must show each and every feature of the claimed invention arranged as in the claim. See *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. 193 (Fed. Cir. 1993). That reference must contain sufficient disclosure as to convince one of ordinary skill in the art that the inventor had possession of the invention at the time the reference was filed. When a composition is claimed, an anticipating reference must completely identify the claimed composition, as it is set forth in the claim, and must also provide an enabling disclosure so that one of ordinary skill in the art can, without undue experimentation, make the invention. See In re Sheppard 144 U.S.P.Q. 42 (CCPA 1964). If a reference fails to properly identity the invention or to enable one to make the invention without undue experimentation, that reference does not describe the invention and cannot be an anticipatory reference.

It is submitted that the DePui reference does not anticipate the now claimed invention. It neither identifies the claimed invention, nor does it enable one of ordinary skill in the art to make the invention without undue experimentation.

The DePui patent, assigned to Astra-Zeneca, is directed to an oral pharmaceutical dosage form for a combined therapy against GORD (Gastro Oesophageal Reflux Disease). The dosage form is preferably a

tablet containing an acid suppressing agent (proton pump inhibitors i.e. omeprazol, lansoprazol,...) and a prokinetic agent (i.e. cisapride, mosapride,...).

The main objective of DePui is to provide an oral dosage form simultaneously containing both an acid suppressive agent and a prokinetic agent, but not enteric coating layered preparations of proton pump inhibitors.

In column 2, starting at line 47, DePui describes as obvious that the proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer and specifically refers to U.S. Patent No. 4,786,505 ("the 505 patent") for omeprazole preparations (see col. 2, lines 50-57) with a description of enteric coating layered preparations of proton pump inhibitors.

The '505 patent discloses omeprazole pellets having a core containing omeprazole and an alkaline substance, one or more separating layers, and an outer enteric coating. The separating layer(s) are described as necessary because: *"The omeprazole containing alkaline reacting cores must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discoloration of omeprazole during the coating process or during storage."*(see '505 col. 3, lines 4-8). U.S. Patent No. 4,853,230 (the '230 patent), contains similar disclosure relating to other proton pump inhibitors (see col. 8, line 67 to col. 9, line 4).

Both the '505 (col. 3, lines 36 to 65) and the '230 (col. 8, lines 31 to 61) patents refer to the importance of the presence of an alkaline substance and both contain extensive disclosure as to the necessity of the separating layer because of the acid sensitivity of omeprazole and the negative experiences in bio-studies of compositions without the separating layer. The '505 patent refers to an article "Development of an Oral Formulation of Omeprazole", Scand. J. Gastroentorology, 1985, pgs. 113-120 describing conventional enteric coated dosage forms and their stabilization.

DePui fails to describe how a stable and useful oral form of a proton pump inhibitor can be made without having an alkaline reacting substance and at least one separating layer. That is to say, assuming that DePui contained sufficient disclosure to identify such a composition, it fails to contain enabling disclosure as to how to make such a composition. Further, it never discloses or suggests that the active layer is substantially non-porous. See line 3 of pending claim 1. Importantly, the rejection does not state, or suggest, that the reference shows or suggests this feature of the now claimed invention.

All 14 examples described by DePui refer to a proton pump inhibitor dosage form having an alkaline substance and at least one separating layer between the core and the surrounding enteric coating. The alkaline substance can be included as a basic salt of the corresponding proton pump inhibitor, i.e. omeprazole

magnesium salt, as stated in the '505 (col. 4, lines 23 to 27) and '230 (col. 8, lines 55 to 61) patents. The references examples merely refer to the active layer being applied to the seed in a fluidized bed apparatus. There is not a single example, suggestion, description or mention of how to produce a stable and useful composition or composition with a substantially non-porous active layer as defined in the presently pending claims.

The Examiner in the Office Action, has referred to text regarding the enteric coating layer of proton pump inhibitors as "optional" for both the presence of alkaline reacting substances and separating layers(s). However, that "optional" feature is referred to generally and it is not supported by the cited prior art or by the patent description. Since the main object of DePui is a combined therapy for GORD, DePui sought broad protection and attempted to foreclose others from patenting a composition with no separating layer by a uninformative comment as to such a possibility. However, DePui fails to describe how such useful and stable enteric coated dosage forms can be made without separating layer(s).

It is submitted that referring to an embodiment as "optional" does not translate into a disclosure or description of embodiments employing or failing to employ the "option". This is especially true where, as here, the specification contains no written description of such an embodiment, no enabling disclosure of how to make or use the "optional" embodiments and, not only fails to provide a best mode, but fails to disclose any mode.

A mere mention of a possible embodiment is not sufficiently definite or particular that, without undue experimentation, one of ordinary skill in the art can gain possession of the claimed subject matter. See, Sheppard, supra. at page 45. Characterizing a feature as "optional" does not convey to one of ordinary skill in the art that the inventor had possession of that option or all other options. Accordingly, the DePui disclosure is not enabling to prepare stable and useful proton pump inhibitor oral dosage forms without having at least a separating layer. Hence there can be no anticipation.

During the June 10, 2003 interview, the Examiners indicated that they were not maintaining that DePui disclosed a stable dosage form without a separating layer but only that one could follow the DePui examples and just omit the steps leading to the inclusion of the separating layer. Such literalism seems to contravene the very purpose of the patent laws, i.e. to advance the useful arts.

DePui is not the only document to generically refer to two-layered granules containing anti-ulcer benzimidazole compounds.

The PCT International Search Report (ISR) for WO 99/06032 cited example 6 of EP 642797 ("Takeda") as the closest prior art. That reference was submitted to the Examiner herein with the filing of the application.

Takeda relates to pharmaceutical compositions containing two different active compounds:

- an antibacterial substance (not related to benzimidazole anti-ulcer compounds), and

- an anti-ulcer substance of the same kind as described in the patent application, being the pharmaceutical composition a gastrointestinal mucosa-adherent solid preparation.

The antibacterial substance is an antibiotic, e.g. amoxicillin, against *Helicobacter pylori* (HP), a bacteria which promote gastric ulcers. The anti-ulcer substance, e.g. lansoprazole, acts on the eventually formed ulcers.

According to Takeda, the pharmaceutical compositions must be adherent to the gastric mucosa, causing it to remain for a longer period in the gastrointestinal tract and hence to improve the bioavailability of active ingredients. To obtain this result Takeda teaches mixing any of two active substances, or previous oral forms containing them, with material showing adherence to the gastric mucosa. The only reference in Takeda to multi-layered granules containing anti-ulcer benzimidazole compounds is example 6 of pages 16 and 17, which literally reads as follows:

Example 6

Production of a formulation comprising lansoprazole and a gastrointestinal mucosa-adherent solid prepration containing AMOX

1) Granules containing lansoprazole was prepared as follows:

Ingredients	Mg
Lansoprazole	30
Magnesium Carbonate USP	22.4
Sugar Spheres NF	110.0
Sucrose NF	59.8
Starch NF	36.4
Low-Substituted Hydroxypropyl Cellulose NF (L-HPC-31)	40.0
Hydroxypropyl Cellulose NF (HPC-L)	1.4
Methacrylic Acid Copolymer LD (Eudragit L30D-55) (Röhm Pharma Co.)	44.6
Polyethylene Glycol NF (PEG-6000)	4.4
Titanium Dioxide USP	4.4
Polysorbate 80 NF (Rheodol TW-0120)	2.0
Talc USP	14.0
Colloidal Silicon Dioxide NF (Aerosil)	0.6
Purified water* USP	q.s.
Total	370.0
*: Removed during the manufacturing process USP; The United States Pharmacopeia NF: The National Formulary	

Sugar spheres were coated with a mixture of lansoprazole, magnesium carbonate, sucrose, starch and L-HPC-31 by means of spraying aqueous HPC-L solution in a centrigual fluid-bed granulator (CF-1000S, Freund Co.) and the resultant wet granules were dried in a vacuum oven at about 40°C for about 18 hours, and then sieved. The obtained granules were coated with aqueous enteric Eudragit suspension containing PEG-6000, talc, titanium dioxide and Rheodol TW-0120 in a fluid-bed coater (F10-Coater FLO-80, Freund Co.), and sieved, and then dried in a vacuum oven at about 42°C for about 18 hours. The obtained granules were mixed with talc and Aerosil.

2) 370 mg of granules containing lansoprazole as obtained in 1) above and 100 mg of gastrointestinal mucosa-adherent solid preparation containing AMOX as obtained in Reference Example 3 were packed in No. 0 capsules to yield a capsule preparation.

Both the PCT ISR and IPER, specifically pointed to example 6 of the Takeda patent.

Accordingly, the above example 6, obviously its point 1, was considered as the closest prior art to the patent application, because it was the only prior description of two-layered granules (an inert core and two layers) containing anti-ulcer benzimidazole compounds (lansoprazole).

Following the IPER, an experimental protocol was undertaken trying to reproduce the lansoprazole granules supposedly described in the example 6 of the Takeda's patent.

Previously submitted was the Declaration by Dr. Molina, Mr. Picornell and Mr. Bravo, three pharmaceutical technology experts. Mr. Picornell is also the inventor of the patent application. Set forth in the Declaration are the attempts to reproduce example 6 of Takeda. The declarants even attempted to correct the defects of the procedure of example 6. The experimental work done by the above-mentioned declarants led to the following conclusion:

> *"Therefore, even after correcting the defect of the procedure described in section 1) of example 6 of European Patent Application EP 0 642 797 in relation to the quantity of binder material, this procedure does not yield enteric-coated gastrointestinal granules of lansoprazole that are appropriate and acceptable from the pharmaceutical standpoint. Consequently, the use of the above procedure does not yield granules equal or similar to those obtained with the procedure contemplated in Patent Application PCT WO/06032, particularly as described in example 1 therein."*

The presently claimed oral pharmaceutical preparations are two-layered substantially spherical granules, with a homogenous active charge layer and a substantially non-porous surface. While acid-resistant, they dissolve rapidly in alkaline medium.

The previously submitted declaration shows that such two-layered granules are not obtainable by the procedure described in example 6 of Takeda, even introducing modifications to correct the defects of the example 6 procedure.

As can be seen, the preparation of compositions of the type now claimed is not a trivial matter. DePui's cavalier attitude in failing to include a description or example of how to produce a dosage form without a separating layer should not be considered as an enabling disclosure. Takeda provides substantially more detail for the example 6 procedure than the passing mention of DePui of an embodiment with no separating layer. Accordingly, there is no basis in the record to consider DePui as enabling of the now claimed invention.

The Office Action never addresses the substance of the declaration which is evidence and must be considered. Rather, the Office Action dismisses the declaration stating that it compares a related foreign application with "this EP reference" which is not a basis relied upon by the Examiner. However, the evidence must be considered whether the Examiner is relying on the reference or not because the art must considered as a whole.

On page 6 of the Official Action, the Examiner calls for a showing with respect to the stability of compounds. The Examiner appears to be raising an issue as to the adequacy of the disclosure with respect to

the classes of compounds. However, the Examiner does not identify what the basis is for calling for the showing or questioning the enablement or operability of the claimed invention with respect to the classes of compounds recited in claim 1. Unless the Examiner can set forth on the record concrete reasons for questioning the adequacy of disclosure or operability, it is improper for the Examiner to state that applicant has not shown that one can formulate a stable composition with each of the claimed classes of active compounds. It should be noted that the claims of the DePui reference appear to encompass a far more extensive number of classes of compounds yet only 14 examples have been provided none which even address the embodiment wherein there is no separating layer. The PTO cannot employ a double standard.

Claims 1 to 13 and 15 to 36 have been rejected under 35 U.S.C. 103(a) as patentable over DePui in view of comments set forth in the Official Action in the paragraph on the bottom of page 7 thereof. However, the Examiner after discussing the disclosure of DePui concludes that one of ordinary skill in the art would have been motivated to make an oral composition comprising an inert core, an active coating, and an enteric coating without the presence of a separating layer based on the reference and the expected result would be a successful composition for the treatment of gastrointestinal disorders. However, the Examiner never sets forth what criteria or what basis there is to believe that the resulting composition would be "successful". Applicants have submitted extensive material showing that one would have expected to the contrary, that is in the absence of the separating layer, that the composition would not be "successful" whatever is meant by that term as employed by the Examiner. To the contrary, based on the submissions, one would have expected failure. This is because as discussed above, DePui does not contain a single example that prepares such a composition and contains no information as to how such a composition would actually perform. Curiously, DePui does not even include stability information in the formulations of the 14 examples.

Claims 1 and 35 have been rejected under 35 U.S.C. §103 as unpatentable over DePui in view of Lovgren et al., EP 0 244 380 B1. It is submitted the rejection is improper and should be withdrawn.

The Lovgren reference teaches the necessity of the separating layer. Therefore, to combine this reference with DePui is improper since a vital and important part of the Lovgren reference would have to be disregarded. Clearly, the Examiner is engaging in a pick and choose technique to formulate an obviousness rejection based on hindsight reconstruction. This is improper under 35 U.S.C. §103. Also see In re Ratti 123 U.S.P.Q. 349 (CCPA, 1959).

Applicants submit there is a sufficient side by side showing of record by comparing some of the U.S. 6,132,771 examples with some of the examples of '505 patent.

Attached ***Annex 1*** includes a chart comparing example 9 of the '771 patent with Examples 7, 8 and Comparative Example V of the '505 patent. A comparison of the method to produce magnesium omeprazole pellets of the Example 9 of the '771 patent and the method to produce the pellets of Examples 7 and 8 of the '505 show that the **processes are identical**. See ***Annex 2***.

The core material of Example 9 of the '771 patent has the same ingredients as the core material of Example 7 ('505 patent), the only difference being the ratio of magnesium omeprazole versus diluents, which is higher in Example 9. In both cases the core material is covered with hydroxypropylmethylcellulose and the percentage of the polymeric film forming material used in the separating layer is essentially the same (11 and 10% respectively).

Finally, pellets covered with separating layer are further covered with an enteric polymer and the ratio of that polymer used in the enteric layer in both cases are essentially the same (11 and 10%, respectively). In order to calculate the % of methacrylic acid copolymer, one can assume that the material used is 100g of a 30% aq. suspension of the polymer.

The formulation of Example 8 of the '505 patent is the same formulation of Example 7, wherein part of the mannitol diluent has been substituted by magnesium hydroxide.

As stated in column 13, lines 40 to 65 of the '505 patent, the formulation of the Comparative Example V is the same as in Example 8 but no subcoating layer is used and the pellets are prepared as described in Example 2.

Annex 3 is a chart comparing Example 14 of the '771 patent with Examples 2, 3, 4 and Comparative Examples I, II and III of the '505 patent.

Example 14 of the '771 patent shows an omeprazole formulation identical in respect to the core material to those of Examples 2, 3 and substantially similar to that of Example 4 of the '505 patent. In the latter example, sodium lauryl sulphate has been replaced by a different surfactant, Pluronic F 68. In Example 14 ('771 patent) the core material is further coated with a film coating polymer (hydroxypropylcellulose) used in a ratio of 8% whereas in Examples 2, 3 and 4 ('505 patent), the film forming coating polymer (hydroxypropyl methyl cellulose or polyvinylpirrolidone) is used in a 4 or 6% ratio.

Finally, in all the above cases, pellets with a separating layer are further coated with enteric polymer, used in 8-10% ratio.

Again, the method to prepare omeprazole formulations of Example 14 of U.S. 6,132,771 and of Examples 2, 3 and 4 of the '505 patent is the same.

The formulations of Comparative Examples I, II and II are identical or substantially similar to those of Examples 2, 3 or 4 ('505 patent) but lack the separating layer.

Table 5 (column 14, lines 18 to 41 of the '505 patent) lists various parameters such as acid resistance and storage stability of the Examples 2 to 8 preparations (formulations with separating layer) and of Comparative Example I-V preparations (without separating layer). This comparison shows stability problems or unacceptable low resistance to dissolution in acid media, whereas the preparations with a separating layer have good gastric juice resistance and stability (see column 14, lines 64-68 and column 15 lines 1 to 31 of the '505 patent).

All example pellets of the '771 patent have a separating layer. Some of the examples of the '771 patent are identical or very close to the preparations of the '505 patent. In the '505 patent, there is a side by side comparison of preparations with and without separating layer and it is well established that those lacking separating layer have problems. The '771 patent does not give any information as how to avoid the stability and acid resistance problems of the formulations lacking separating layers and therefore, one of the skill in the art would not be encouraged or expect from the '771 in view of the '505 to prepare a stable formulation lacking a separating layer.

Therefore, the stability difference in the DePui formulation where the drug dosage form is prepared with and without a separating layer has already been established by the '505 patent which is of record

During the course of the telephone interview, applicant's undersigned counsel discussed using the above comparison to show that the disclosure of the DePui was insufficient and that one ordinary skill in the art could not, based on the DePui reference achieve a stable product. It is submitted that the above showing is sufficient. See *In re Fouche* 169 U.S.P.Q. 429, 433 (CCPA 1971).

In view of the foregoing, reconsideration and allowance of the application with claims 1 to 13 and 15 to 40 are earnestly solicited.

The extra claim fee of $36.00 due is to be charged to the Deposit Account mentioned below.

It is believed that no fees or charges are required at this time in connection with the present application; however, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
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	Ex 6
core material	
Magnesium omeprazole	600
Mannitol	1000
Microcryst. cellulose	300
Sodium lauryl sulphate	6
separating layer	
core material	400
hydroxypropylmethylcellulose	48
Enteric coating layer	
pellets with separating layer	200
Methacrylic acid copolymer	100
Triethyl citrate	30
Mono and di glycerides (NF)	5
Polysorbate 80	0,5

	Ex 7	Ex 8	Comp Ex V
core material			
Magnesium omeprazole	222	222	222
Mannitol	1673	1473	1473
Microcryst. cellulose	100	100	100
Sodium lauryl sulphate	5	5	5
Magnesium hydroxide		200	200
separating layer			
core material	500	500	0
hydroxypropylmethylcellulose	20	20	0
Enteric coating layer			
pellets with separating layer	500	500	500
Hydroxypropyl methyl cellulose phthalate	20	20	57
cetyl alcohol	3	3	3

ANNEX 1

Example 9

Preparation of enteric coating layered pellets by extrusion/spheronization.

Core material	
Magnesium omeprazole	600 g
Mannitol	1150 g
Microcrystalline cellulose	300 g
Hydroxypropyl cellulose	100 g
Sodium lauryl sulphate	6 g
Water purified	802 g
Separating layer	
Core material	400 g
Hydroxypropyl methylcellulose	48 g
Water purified	960 g
Enteric coating layer	
Pellets covered with separating layer	200 g
Methacrylic acid copolymer	200 g
Triethyl citrate	30 g
Mono- and diglycerides (NF)	5 g
Polysorbate 80	0.5 g
Water purified	309 g

Sodium lauryl sulphate is dissolved in purified water to form the granulation liquid. Magnesium omeprazole, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-mixed.

The wet mass is forced through an extruder equipped with screens of size 0.5 mm. The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered by a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose/water solution.

The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus.

Example 7 and 8

Formulations with the magnesium salt of omeprazole.

		Example No 7	Example No 8
Uncoated pellets			
I	Omeprazole magnesium salt	222 g	222 g
	Mannitol powder	1 673 g	1 473 g
	Microcrystalline cellulose	100 g	100 g
	Magnesium hydroxide	—	200 g
II	Sodium lauryl sulphate	5 g	5 g
	Distilled water	500 g	375 g

The preparation was made as described in Example 2 with the exception that the omeprazole magnesium salt was added together with the other ingredients in mixture I.

		Example 7 and 8
Subcoated pellets		
III	Uncoated pellets	500 g
	Hydroxypropyl methylcellulose	20 g
	Distilled water	400 g

The pellets were prepared as described in Example 2.

		Example 7 and 8
Enteric coated pellets		
IV	Subcoated pellets	500 g
	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The enteric coated pellets were prepared as described in Example 2.

Example 2

Uncoated pellets		
I	Mannitol powder	16 150 g
	Lactose anhydrous	800 g
	Hydroxypropyl cellulose	600 g
	Microcrystalline cellulose	450 g
II	Omeprazole	2 000 g
	Sodium lauryl sulphate	50 g
	Disodium hydrogen phosphate	80 g
	Distilled water	4 400 g

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing suspended omeprazole was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

Subcoated pellets		
II	Uncoated omeprazole pellets	6 000 g
	Hydroxypropyl methylcellulose	240 g
	Distilled water	4 800 g

The polymer solution (III) was sprayed on the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

Enteric-coated pellets		
IV	Subcoated pellets	500 g
	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5% the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 125 mg, corresponding to 20 mg of omeprazole. 30 capsules were packed in tight containers together with a desiccant.

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Ex 14	
core material	**g (%)**
Omeprazole	225(12)
Mannitol	1425(77)
Microcryst. cellulose	40(2)
Sodium lauryl sulphate	5(0.2)
hydroxypropyl cellulose	60(3.2)
lactose anhydrous	80(4.3)
Disodium hydrogen phosp	8(0.4)
separating layer	
core material	300
hydroxypropyl cellulose	30(8)
talc	51
Magnesium stearate	4
Enteric coating layer	
pellets with separating layer	300
Methacrylic acid copolymer	140(10)
Triethyl citrate	42
Mono and di glycerides (NF)	7
Polysorbate 80	0.7

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	Ex 2	Ex 3	Ex 4	Comp Ex I	Comp Ex II	Comp Ex III
core material	**g (%)**	**g (%)**	**g (%)**	**g (%)**	**g (%)**	**g (%)**
Omeprazole	2000(10)	200(10)	200(10)	200(10)	200(10)	200(10)
Mannitol	16150(80)	1620(80)	1610(80)	1610(80)	1610(80)	1610(80)
Microcryst. cellulose	400(2)	40(2)	40(2)	40(2)	40(2)	40(2)
Sodium lauryl sulphate	50(0.2)	1(0.05)				
hydroxypropyl cellulose	600(3)	60(3)	60(3)	60(3)	60(3)	60(3)
lactose anhydrous	800(4)	80(4)	80(4)	80(4)	80(4)	80(4)
Disodium hydrogen phosphate	80(0.3)	9,3(0.4)	24(1)	2(0.1)	8(0.4)	24(1)
Pluronic F68			10(0.5)	10(0.5)	10(0.5)	10(0.5)
separating layer						
core material	6000	500	500			
hydroxypropyl cellulose						
talc						
Magnesium stearate						
hydroxypropyl methyl cellulose	240(4)					
Polyvinylpirrolidone		20(4)	30(6)			
Enteric coating layer						
pellets with separating layer	500	500	500	500	500	500
Methacrylic acid copolymer						
Triethyl citrate						
Mono and di glycerides (NF)						
Polysorbate 80						
Hydroxypropyl methyl cellulose pht	57(10)	45(8)	45(8)	45(8)	45(8)	45(8)
cetyl alcohol		3	5	5	5	5

ANNEX 3